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First Named Inventor	Walke
Group Art Unit	1646
Examiner Name	O. Chernyshev
Attorney Docket Number	LEX-0135-USA

ENCLOSURES *(check all that apply)*

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SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT

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Date	March 5, 2004

CERTIFICATE OF MAILING

I hereby certify that this correspondence is being deposited with the United States Postal Service with sufficient postage as Express mail label EV322477435US addressed to: Commissioner for Patents, MS Appeal Brief - Patents, P.O. Box 1450, Alexandria, VA 22313 on: March 5, 2004

Typed or printed name	Nancy Stacey		
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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Appellant(s):	Walke *et al.*	Group Art Unit: 1646
Application No.:	09/783,669	Examiner: O. Chernyshev
Filed:	02/14/01	Att Docket No.:LEX-0135-USA
Title:	Novel Human 7TM Proteins and Polynucleotides Encoding the Same	

REPLY BRIEF

Mail Stop Appeal Brief - Patents
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REPLY BRIEF

Sir:

Appellants hereby submit an original and two copies of this Reply Brief to the Board of Patent Appeals and Interferences ("the Board") in response to the Examiner's Answer mailed on January 5, 2004 which is due on March 5, 2004. This Reply Brief is thus timely submitted.

Appellants believe no additional fees are due in connection with this Reply Brief. However, should any additional fees under 37 C.F.R. §§ 1.16 to 1.21 be required for any reason related to this communication, the Commissioner is authorized to charge any underpayment or credit any overpayment to Lexicon Genetics Incorporated Deposit Account No. 50-0892.

I. REAL PARTY IN INTEREST

Appellants agree with the Examiner's assertion that "A statement identifying the real party in interest is contained in the brief" (Examiner's Answer at page 2).

II. RELATED APPEALS AND INTERFERENCES

Appellants agree with the Examiner's assertion that "A statement identifying the related appeals and interferences which will directly affect or be directly affected by or have a bearing on the decision in the pending appeal is contained in the brief" (Examiner's Answer at page 2).

III. STATUS OF THE CLAIMS

Appellants agree with the Examiner's assertion that "The statement of the status of the claims contained in the brief is correct" (Examiner's Answer at page 2).

IV. STATUS OF THE AMENDMENTS

Appellants agree with the Examiner's assertion that "The appellant's statement of the status of

amendments after final rejection contained in the brief is correct" (Examiner's Answer at page 2).

V. SUMMARY OF THE INVENTION

Appellants agree with the Examiner's assertion that "The summary of invention contained in the brief is correct" (Examiner's Answer at page 2).

VI. ISSUES ON APPEAL

Appellants agree with the Examiner's assertion that "The appellant's statement of the issues in the brief is correct" (Examiner's Answer at page 2).

VII. GROUPING OF THE CLAIMS

Appellants agree with the Examiner's assertion that "Appellant's brief includes a statement that the claims stand or fall together" (Examiner's Answer at page 2).

VIII. CLAIMS APPEALED

Appellants agree with the Examiner's assertion that "The copy of the appealed claims contained in the Appendix to the brief is correct" (Examiner's Answer at page 2).

IX. PRIOR ART OF RECORD

Appellants agree with the Examiner's assertion as to the art previously presented by the Examiner in this case (Examiner's Answer at page 3).

X. ARGUMENT

A. Do Claims 1-7 Lack a Patentable Utility?

Appellants do not wish to restate all of the arguments presented in the Appeal Brief concerning the Examiner's allegation that claims 1-7 lack a patentable utility, and instead incorporate the entirety of Section VIII(A) of the Appeal Brief at this point herein by reference. However, Appellants feel the need to specifically address several of the arguments presented in the Examiner's Answer in some detail for the record.

The Examiner is attempting to reject the present application based on the position that the claimed invention lacks a specific and substantial utility for has been made. Appellants strongly disagree. While the Examiner appears to recognize the importance and utility of GPCRs as a class and as a target for pharmaceutical products, the Examiner's Answer maintains that the patentable utility of the sequences of the present invention which encode a GPCR, that was identified as MRGX2, is in question as no biological function has been described. While the Examiner's Answer (page 7, lines 10-11) suggests that the relationship between the GPCR of the present invention and the molecule identified by third party scientists, wholly unaffiliated with Applicants, as encoding *Homo sapiens* G protein-coupled receptor MRGX2 (GenBank accession no. NM_054030) has was first presented in the Appeal Brief, Appellants note that the relationship was described previously in both the Response filed on August 29, 2002 (paper no.11) and in the Response to Final.

The Examiner's Answer (page 3) states that "It is clear from the instant specification that the protein described therein is what is termed an "orphan protein" in the art. However, the GPCR protein encoded by the sequences of the present invention is not an orphan protein. It might, however, be referred to as an "orphan receptor", as the native ligand which this GPCR binds was not identified in the application as filed. This does not, as the Examiner's Answer asserts (on page 15), support the position that one of skilled in the art would not recognize the utility of the present invention and would not be able to use the sequences of the present invention in a multitude of ways, for example, in drug discovery. One of skill in the art would readily recognize that they not need know the native ligand for the present receptor (nor any receptor) to utilize the sequences of the present invention which encode said receptor in drug discovery. Using the

methods described in the specification those of skill in the art would be able to use the sequences of the present invention to construct a transgenic "knockout" mouse. Furthermore, those of skill in the art using the guidance provided by the specification would be able to use the sequences of the present invention to prepare a recombinant receptor protein used to screen for an agonist or antagonist "drug". Thus the sequences of the present invention have clear use in drug discovery utility could be carried out using the methods described in the specification and known to those of skill in the art. All of these uses, and others, can be realized without knowledge of the receptor's native ligand.

The Examiner's Answer also reiterates the Examiner's previously stated position that sequence homology and the relationship between structure and function is not generally accepted by those of skill in the art. In support of this position the Examiners Answer goes on to describe again several contrarian articles that have been both previously presented and rebutted by the Appellant. None of these articles constitute direct evidence that Appellants assertion that the sequences of the present invention encode the GPCR, MRGX2 is not credible as none of the cited articles describe the protein of the present invention.

The Examiner's Answer first reiterates an article by Ji, *et al.* ("Ji"; 1998, J. Biol. Chem. *273*:17299-17302) as teaching that structural homology alone is not a good predictor of function. But an exact quote from Ji, completely undermines this argument: "a substantial degree of amino acid homology is found between members of a particular subfamily, but comparisons between subfamilies show significantly less or no similarity" (Ji, at 17299, first paragraph, emphasis added). This quote suggests that homology with members of a G-protein coupled receptor is indicative that the particular sequence is in fact a member of that subfamily.

The Examiner's Answer also reiterates an article by Skolnick, *et al.* (Trends in Biotech *18*:34-39, 2000). However, Skolnick, *et al.* concerns predicting protein function not by overall amino acid homology to other family members, but instead concerns prediction of function based on the presence of certain functional "motifs" present within a given protein sequence. Thus, Skolnick does not apply to the current situation, where overall protein homology is used to assign function to a particular sequence. However, even in the event that Skolnick were applicable, Skolnick itself concludes that "sequence-based approaches to protein-function prediction have proved to be very useful" (Skolnick at page 37), admitting

that such methods have correctly assigned function in 50-70% of the cases, thus a majority of the time supporting rather than refuting Applicants assertions.

Finally the Examiner's Answer also reiterates an article by Yan *et al.* ("Yan"; 2000, Science 290:523-527). However, this paper cites only one example, two isoforms of the anhidrotic ectodermal dysplasia (EDA) gene, where a two amino acid change conforms one isoform (EDA-A1) into the second isoform (EDA-A2). However, while it is true that this amino acid change results in binding to different receptors, it is important to note that the different receptors bound by the two isoforms are in fact related (Yan at page 523). Furthermore, the EDA-A2 receptor was correctly identified as a member of the tumor necrosis factor receptor superfamily based solely on sequence similarity (Yan at page 523). Thus, Yan is hardly indicative of a high level of uncertainty in assigning function based on sequence, for that is the approach chosen by the authors and it thus also does not support the alleged lack of utility of the sequences of the present invention.

In summary a careful reading of the cited "relevant literature" does not in fact support the concept that function cannot be based on sequence and structural similarity, in contrast many of the examples actually support the use of such methodologies while identifying several areas in which caution should be exercised. As stated previously these inaccuracies and potential pitfalls can be overcome by a more careful analysis by those of skill in the art. Automatic methods of sequence homology identification was only the staring point for consideration the sequences of the present invention underwent careful analysis by a series of individuals of skill in the art, many highly qualified (multiple B.S. and Ph.D. level scientists).

As stated previously, while there may not be a 100% consensus within the scientific community regarding prediction of protein function from homology information, this is not unusual nor is it indicative of a general lack of consensus. These articles are just examples of the few contrarian (erroneously described as spurious) articles that the PTO has repeatedly attempted to use to deny the utility of nucleic acid sequences based on a small number of publications that call into doubt prediction of protein function from homology information and the usefulness of bioinformatic predictions. A few rare exceptions do not a rule make.

One form of evidence supporting the position that bioinformatic information is recognized to be of

value by those of skill in the art is the results of a recent search of the NCBI-NLM-NIH public scientific database "PubMed" using the term "bioinformatics" which resulted in 5,548 different scientific publications (these will not be provided to avoid burdening the USPTOs scanning group). If bioinformatic information is not useful in predicting protein function from structural homology information, why are so many publications reporting the results of its use?

A second form of evidence supporting the position that bioinformatic information is recognized to be of value by those of skill in the art is the fact that many scientists, corporations and institutions elect to allocate significant proportions of their limited resources for access to private bioinformatic systems and databases. Thus, it would appear obvious that those of skill in the art value and accept the results of bioinformatic analysis for they are willing to pay dearly for access to such information.

A third, an perhaps most persuasive form of evidence supporting the position that bioinformatic information is recognized to be of value by those of skill in the art is the issuance of multiple US patents regarding bioinformatic prediction and methods for doing the same (see for example, U.S. Patent Nos. 6,229,911, 6,567,540, 6,615,141, 6,631,331, 6,651,008, 6,677,114, these patents will not be provided to avoid burdening the USPTOs scanning group). Of particular interest might be U.S. Patent No. 6,466,874, one of whose claims reads "A method of identifying proteins as functionally linked, the method comprising comparing sequences to find homologous functional domains." Why would a U.S. Patent have issued on a method of carrying out an analysis that is without utility, because it is not accepted by those of skill in the art as a credible method of predicting protein function from structural homology information?

Appellants respectfully point out that, as discussed above, the legal test for utility simply involves an assessment of whether those skilled in the art would find any of the utilities described for the invention to be believable. Appellants submit that the overwhelming majority of those of skill in the relevant art would believe prediction of protein function from homology information and the usefulness of bioinformatic predictions to be powerful and useful tools. Clearly the several forms of evidence presented, and certainly the issuance of U.S. Patents suggest that those of skill in the art recognize the utility of bioinformatic analysis and its credibility in assessing structure function relationships. Thus the vast majority of those of skill in the art would believe that Appellants sequence is a GPCR, a variant of MRGX2.

The Examiner's Answer also discounts several arguments concerning the utilities of the sequences of the present invention since other nucleic acid sequences can be used in a similar fashion. In addition to the detailed arguments presented by Appellants in the Appeal Brief with regard to each of these asserted utilities, Appellants once again point out that these arguments are completely rebuffed by the Federal Circuit's holding in *Carl Zeiss, supra* ("[A]n invention need not be the best or only way to accomplish a certain result").

The main argument concerning this utility and that of use of the specific sequences on DNA chips is that since other nucleic acid sequences can be used to map the human chromosome or on DNA chips, the use of these specific sequences on DNA chips does not have specific or substantial utility. The Examiner further equates such utilities as chromosome mapping as comparable to "conceding that any object of fixed mass has *prima facie* utility as a molecular weight standard, irrespective of any other properties possessed by that object"(Examiner's Answer at page 13). Such an analogy comparing the utility of human chromosome mapping with a utility that USPTO has deemed as a "throw away' utility is preposterous. Among other things the mapping of the relatively few expressed human genes to a particular chromosome has long been a recognized method of identifying a genes associated with particular diseases. Furthermore, the mapping of the human chromosome is a project of such widely recognized importance by those of skill in the art and even lay people, that both the US government and private corporations have dedicated millions of dollars to such a project. One must ask, if the mapping of human chromosomes is a throw away utility then why has the US government spent so many taxpayer dollars on this project?

With regards to the position that because there are other objects having the same utility, that utility has been rendered generic and therefore invalid begs the question, previously presented, that don't all golf balls and tires have the same utility of other golf balls or tires, i.e. they can be used as golf balls or tires respectively and yet these items are readily considered to have patentable utility.

Furthermore, it has been clearly established that a statement of utility in a specification must be accepted absent reasons why one skilled in the art would have reason to doubt the objective truth of such statement. *In re Langer*, 503 F.2d 1380, 1391, 183 USPQ 288, 297 (CCPA, 1974; "*Langer*"); *In re Marzocchi*, 439 F.2d 220, 224, 169 USPQ 367, 370 (CCPA, 1971). As clearly set forth in *Langer*:

> As a matter of Patent Office practice, a specification which contains a disclosure of utility which corresponds in scope to the subject matter sought to be patented must be taken as sufficient to satisfy the utility requirement of § 101 for the entire claimed subject matter unless there is a reason for one skilled in the art to question the objective truth of the statement of utility or its scope.

Langer at 297, emphasis in original. As set forth in the MPEP, "Office personnel must provide evidence sufficient to show that the statement of asserted utility would be considered 'false' by a person of ordinary skill in the art" (MPEP, Eighth Edition at 2100-40, emphasis added). Thus, the present claims clearly meet the requirements of 35 U.S.C. § 101.

Appellants respectfully point out that knowledge of the exact function or role of the presently claimed sequence is not required for use of these sequences on DNA chips to track expression patterns. Given the widespread utility of such "gene chip" methods using *public domain* gene sequence information, there can be little doubt that the use of the presently described *novel* sequences, which provide a specific marker for gene expression of a novel GPCR would have great utility in such DNA chip applications. In fact some such gene chips have contained randomly generated sequence, clearly identified sequences with know expression patterns are of particular value in such analyses. The Examiner agrees that such "DNA chips" have utility, as evidenced by hundreds of issued U.S. Patents, but argues that specific sequences which clearly increase the utility of a patented invention do not. It must be noted that this position runs counter to that made by the Examiner regarding golf balls, wherein the presence of a specific feature that enhances the utility of the golf ball has utility.

Finally, while accepting the Examiner's right to withhold comment and with full recognition of the fact that all patent applications are examined on their own merits and that the prosecution of one patent does not effect the prosecution of another patent, *In re Wertheim,* 541 F.2d 257, 264, 191 USPQ 90, 97 (CCPA 1976), however the issue at hand in one of whether the fact that patents have issued recognizing the utility of a class of molecules does this confers a statutory precedent of patentability to a broad class of compositions. Thus, there remains a lingering issue regarding due process and equitable treatment under the law. While Appellants are well aware of the new Utility Guidelines set forth by the USPTO, Appellants respectfully point out that the current rules and regulations regarding the examination of patent applications is and always has been the patent laws as set forth in 35 U.S.C. and the patent rules

as set forth in 37 C.F.R., not the Manual of Patent Examination Procedure or particular guidelines for patent examination set forth by the USPTO. Furthermore, Appellants respectfully submit that it is the job of the judiciary, not the USPTO, to interpret these laws and rules. Appellants are unaware of any significant recent changes in either 35 U.S.C. § 101, or in the interpretation of 35 U.S.C. § 101 by the Supreme Court or the Federal Circuit that is in keeping with the new Utility Guidelines set forth by the USPTO. Given the rapid pace of development in the biotechnology arts, it is difficult for the Appellants to understand how an invention fully disclosed and free of prior art at the time the present application was filed, could somehow retain *less* utility and be *less* enabled than prior inventions that were issued U.S. patents (which were filed during a time when the level of skill in the art was clearly lower). Simply put, it stands to reason that Appellants invention is *more* enabled and retains *at least as much* utility as the inventions described in the claims of the U.S. patents of record in the Appeal Brief. Thus, holding Appellants invention to a different standard of utility appears inconsistent and inequitable, such a judgement being arbitrary and capricious, a violation of due process and equal protection under the law.

For each of the foregoing reasons, as well as the reasons set forth in the Appeal Brief, Appellants submit that the rejection of claims 1-7 under 35 U.S.C. § 101 should be overruled.

B. Are Claims 1-7 Unusable Due to a Lack of Patentable Utility?

Regarding the rejection of claims 1-7 under 35 U.S.C. § 112, first paragraph, since allegedly one skilled in the art would not know how to use the invention, as the invention allegedly is not supported by either a clear asserted utility or a well-established utility, Appellants submit that as claims 1-7 have been shown to have "a specific, substantial, and credible utility", as detailed in Section X(A) above, as well as Section VIII(A) of the Appeal Brief, the present rejection of claims 1-7 under 35 U.S.C. § 112, first paragraph, cannot stand.

Appellants therefore submit that the rejection of claims 1-7 under 35 U.S.C. § 112, first paragraph, must be overruled.

XI. CONCLUSION

Appellants respectfully submit that, in light of the foregoing arguments, the Final Action's conclusion that claims 1-7 lack a patentable utility and are unusable by the skilled artisan due to a lack of patentable utility is unwarranted. It is therefore requested that the Board overturn the Final Action's rejections.

Respectfully submitted,

Peter G Seferian

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March 5, 2004
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